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Retrovirus Drugs

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Definition

Antiretroviral drugs inhibit the reproduction of retroviruses-viruses composed of RNA rather than DNA. The best known of this group is HIV, human immunodeficiency virus, the causative agent of AIDS.

Purpose

Antiretroviral agents are virustatic agents which block steps in the replication of the virus. The drugs are not curative; however continued use of drugs, particularly in multi-drug regimens, significantly slows disease progression.

Description

There are three main types of antiretroviral drugs, although only two steps in the viral replication process are blocked. Nucleoside analogs, or nucleoside reverse transcriptase inhibitors (NRTIs), such as didanosine (ddI, Videx), lamivudine (3TC, Epivir), stavudine (d4T, Zerit), zalcitabine (ddC, Hivid), and zidovudine (AZT, Retrovir), act by inhibiting the enzyme reverse transcriptase. Because a retrovirus is composed of RNA, the virus must make a DNA strand in order to replicate itself. Reverse transcriptase is an enzyme that is essential to making the DNA copy. The nucleoside reverse transcriptase inhibitors are incorporated into the DNA strand. This is a faulty DNA molecule that is incapable of reproducing.

The non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as delavirdine (Rescriptor), loviride, and nevirapine (Viramune) act by binding directly to the reverse transcriptase molecule, inhibiting its activity.

Protease inhibitors, such as indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), and saquinavir (Invirase) act on the enzyme protease, which is essential for the virus to break down the proteins in infected cells. Without this essential step, the virus produces immature copies of itself, which are non-infectious.

A fourth class of drugs was under clinical trials in 2003. Called fusion inhibitors, they block HIV from fusing with healthy cells. The first to receive FDA approval will likely be a drug called Enfurvitide.

Because HIV mutates readily, the virus can develop resistance to single drug therapy. However, treatment with drug combinations appears to produce a durable response. Proper treatment appears to slow the progression of HIV infections and reduce the frequency of opportunistic infections. One of the most notable advances in recent years has been the success of highly active antiretroviral therapy (HAART). This multidrug approach reduced the risk of opportunistic infections in persons with HIV/AIDS and slowed the progression of the disease and death. Usually, patients receive triple combination therapy, however research in 2003 showed a new once-daily regimen of quadruple therapy effective. The combination included adefovir, lamivudine, didanosine, and efavirenz. In short, the scientific community continues to make rapid advancements in developing and evaluating antiretroviral drug therapy. It is best to keep well informed and frequently check with a physician.

Recommended dosage

Doses must be individualized based on the patient and use of interacting drugs. The optimum combinations of antiretroviral drugs have not been determined, nor is there agreement on the stage of infection at which to start treatment. In fact, starting treatment too early has led to unwanted side effects in some patients or problems with patient readiness to comply. Treatment should begin when the time and circumstances are right.

- **Precautions**

Although the antiretroviral drugs fall into several groups, each drug has a unique pattern of adverse effects and drug interactions. Since the drugs are used in various combinations, the frequency and severity of adverse effects will vary with the combination. Although most drug combinations show a higher rate of adverse events than single drug therapy, some patterns are not predictable. For example, indinavir has been reported to cause insomnia in 3% of patients, however, when used in combination with zidovudine, only 1.5% of patients complained of sleep difficulties.

The most severe adverse effects associated with the protease inhibitors are kidney and liver toxicity. Patients also have reported a syndrome of abdominal distention (selling and expansion) and increased body odor, which may be socially limiting. Hemophilic patients have reported increased bleeding tendencies while taking protease inhibitors. The drugs are pregnancy category B. There have been no controlled studies of safety in pregnancy. HIV-infected mothers are advised not to breast feed in order to prevent transmission of the virus to the newborn.

The nucleoside reverse transcriptase inhibitors have significant levels of toxicity. Lactic acidosis in the absence of hypoxemia and severe liver enlargement with fatty degeneration have been reported with zidovudine and zalcitabine, and are potentially fatal. Rare cases of liver failure, considered possibly related to underlying hepatitis B and zalcitabine monotherapy, have been reported.

Abacavir has been associated with fatal hypersensitivity reactions. Didanosine has been associated with severe pancreatitis. Nucleoside reverse transcriptase inhibitors are pregnancy category C. There is limited information regarding safety during pregnancy. Zidovudine has been used during pregnancy to reduce the risk of HIV infection to the infant. HIV-infected mothers are advised not to breast feed in order to prevent transmission of the virus to the newborn.

Efavirenz has been associated with a high frequency of skin rash, 27% in adults and 40% in children. Nevirapine has been associated with severe liver damage and skin reactions. All of the non-nucleoside reverse transcriptase inhibitors are pregnancy category C, based on animal studies.

Using antiretroviral drugs in combination also helps lower risk of developing viral resistance. Fifty percent of patients who fail antiretroviral therapy are resistant to one class of drug. Recent research into multiple drugs and combinations is promising.

Interactions

Because of the high frequency of drug interactions associated with AIDS therapy, specialized references should be consulted. Use of recreational drugs while on antriretroviral therapy can trigger potentially lethal side effects or negate the positive effects of the therapy.

Saquinavir is marketed in both hard and soft gelatin capsules. Because saquinavir in the hard gelatin capsule formulation (Invirase) has poor bioavailability, it is recommended that this formulation only be used in combination with other drugs which interact to raise saquinavir blood levels. Saquinavir soft gelatin capsules (Fortovase) are the preferred dosage form of this drug.

- **Key Terms:**

Antiviral drugs
Medicines that cure or control virus infections.
Bioavailability
A measure of the amount of drug that is actually absorbed from a given dose.

Hypoxemia
Lower than normal oxygenation of arterial blood.
Immune system
The body's natural defenses against disease and infection.
Inflammation
Pain, redness, swelling, and heat that usually develop in response to injury or illness.
Pancreas
A gland located beneath the stomach. The pancreas produces juices that help break down food and secretes insulin that helps the body use sugar for energy.
Insomnia
A sleep disorder characterized by inability to either fall asleep or to stay asleep.
Mutates
Undergoes a spontaneous change in the make-up of genes or chromosomes.
Pregnancy category
A system of classifying drugs according to their established risks for use during pregnancy. Category A: Controlled human studies have demonstrated no fetal risk. Category B: Animal studies indicate no fetal risk, but no human studies; or adverse effects in animals, but not in well-controlled human studies. Category C: No adequate human or animal studies; or adverse fetal effects ~~in~~ animal studies, but no available human data. Category D: Evidence of fetal risk, but benefits outweigh risks. Category X: Evidence of fetal risk. Risks outweigh any benefits.
Retrovirus
A virus composed of ribonucleic acid (RNA) instead of deoxynucleic acid (DNA).
Virus
A tiny, disease-causing particle that can reproduce only in living cells.

Resources:

Resources

Periodicals

- "Grant Awarded for Evaluation of Once-Daily Antiretroviral." Virus Weekly (November 26, 2002): 12.
- Isaac, A., and D. Pillay. "New Drugs for Treating Drug Resistant HIV-1: Clinical Management of Virological Failure Remains an Important and Difficult Issue for HIV Physicians." Sexualy Transmitted Diseases (June 2003): 176-183.
- Lipsky, James J. "Antiretroviral Drugs for AIDS." The Lancet 348 (September 21, 1996): 800.
- "New Therapy Strategies Focusing on Long Term: Drugs' Impact on Heart is Debated." AIDS Alert (April 2003): 45.
- "Once-Daily Quadruple Regimen Safe, Effective." AIDS Weekly (October 7, 2003): 4.
- "Recreational Drugs can Reduce Safety, Efficacy of Antiretroviral Agents." AIDS Weekly (December 16, 2003): 3.
- Thanker, H.K., and M.H. Snow. "HIV Viral Suppression in the Era of Antiretroviral Therapy." Postgraduate Medical Journal (January 2003): 36.
- Williams, Ann B. "New Horizons: Antiretroviral Therapy in 1997." Journal of the Association of Nurses in AIDS Care 8 (July-August 1997): 26.

Organizations

- Project Inform. 205 13th Street, #2001, San Francisco, CA 94103. (415) 558-8669. http://www.projinf.org.

Other

- AIDS Clinical Trials Information Service website and telephone information line. Sponsored by Centers for Disease Control and Prevention, Food and Drug Administration, National Institute of Allergy and Infectious Diseases, and National Library of Medicine. 800-TRIALS-A (800-874-2572). http://actis.org.
- HIV/AIDS Treatment Information Service website and telephone information line. Sponsored by Agency for Health Care Policy and Research, Centers for Disease Control and Prevention, Health Resources and Services Administration, Indian Health Service, National Institutes of Health, and Substance Abuse and Mental Health Services Administration. 800-HIV-0440 (800-448-0440). http://www.hivatis.org.
- Project Inform National HIV/AIDS Treatment Hotline. 800-822-7422.

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